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| (21) International Application Number: PCT/GB91/02064 (22) International Filing Date: 21 November 1991 (21.11.91) (30) Priority data: 9025711.4 27 November 1990 (27.11.90) GB (71) Applicant (for all designated States except US): BEECHAM GROUP P.L.C. [GB/GB]; SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): DAVIS, Adrian, Francis [GB/GB]; GORDON, Jennifer, Jane [GB/GB]; Smith-Kline Beecham Consumer Brands, St George's Avenue, Weybridge, Surrey KT13 0DE (GB). | | (74) Agent: WHITE, Susan, Mary; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US. Published <i>With international search report.</i> |
| (54) Title: TOPICAL COMPOSITION (57) Abstract Two-component pharmaceutical compositions for topical application to the human or animal body and intended for mixing together on or immediately prior to application, comprising two liquid phases having different lipophilicities and a drug dissolved in at least one of the liquid phases. | | |

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+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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TOPICAL COMPOSITION

The present invention relates to the topical application of active substances to the human or animal body and in particular to two-component compositions intended for mixing together either in situ on application, or immediately prior to application.

The solubility of active substances in solvent systems is important in relation to the design of topical delivery systems. It has been shown that the degree of saturation of an active substance, for example a drug, in the solvent system or vehicle is a determining factor in controlling release of the active substance.

15 Coldman et al.; J. Pharm. Sci., 58, 1098-1102, 1969, demonstrated that percutaneous absorption could be enhanced by over-saturating a drug solution to a supersaturated level. A supersaturated state is generated when the concentration of a solute, for example a drug, in a given solvent system exceeds the saturated solubility of the solute in that system.

Coldman prepared a solution of a drug in a mixture of a volatile and a non-volatile solvent and applied it to the surface of a sample of human skin. The volatile solvent evaporated leaving the drug in solution in the non-volatile solvent at a concentration in excess of its saturated solubility in that solvent, thereby creating a supersaturated solution in situ on the skin surface.

European Patent Publication No. 0 132 674 (EP-A-0 132 674) describes a pharmaceutical composition for generating a drug solution in a supersaturated state which is not reliant on the prior evaporation of a volatile solvent.

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The composition comprises two distinct but miscible liquid phases, at least one of which contains a drug dissolved therein. The composition of the phases is such that each has a different lipophilicity (or polarity) and each confers a different saturated solubility on the drug. The composition of the liquid phases and the concentration of drug in one or both phases is such that on admixture of the two phases, the total drug concentration in the mixture thus formed is greater than the concentration of drug which a mixture of the same composition can accommodate as a saturated solution. On mixing the two liquid phases, the resulting mixture is therefore supersaturated with respect to the drug.

15

It is an inherent property of supersaturated solutions that they will seek to adopt a more thermodynamically stable saturated state. This will generally be achieved by precipitation of solute from the supersaturated solution. The tendency for precipitation and the time scale over which it will occur will be dependent on a number of internal and external factors, including for example the degree of saturation, the nature of solute and solvents, the presence of extraneous material and the ambient temperature.

25

European Patent Publication No. 0 272 045 (EP-A 0 272 045) describes a pharmaceutical composition for generating a supersaturated solution wherein the tendency for drug precipitation to occur is substantially reduced by incorporation of an antinucleating agent into at least one of the liquid phases of compositions described in EP-A 0 132 674.

It has now been found that duration of the supersaturated state, generated by certain two phase compositions in accordance with EP-A 0 132 674, is limited by solvent

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evaporation taking place after mixing together of the two liquid phases, for example after topical administration of the resulting supersaturated drug preparation in the form of a thin film intended for long contact time usage.

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Solvent evaporation poses a particular problem with two-phase compositions as described in EP-A 0 132 674 which are formulated with a high water content.

- 10 Preferential evaporation of a more volatile solvent, such as water, after mixing of the two liquid phases has the effect of increasing the saturated solubility of the drug in the resultant mixture. An increase in drug saturated solubility is reflected in a reduction of the degree of saturation of
15 the supersaturated drug solution.

Placebo bases with a high water content, for example hydrophilic creams and gels, are widely used in the formulation of topical preparations for delivery of
20 topically active substances, in particular lipophilic drugs.

It has now been found that the degree of saturation in supersaturated solutions generated from pharmaceutical compositions according to EP-A 0 132 674 can be sustained by
25 using a novel range of solvent compositions which counterbalance the deleterious effects of water loss due to evaporation.

Compositions of the present invention as hereinafter defined
30 therefore have practical utility in the field of topical drug administration, in particular where use of thin films over long contact times is necessary or advantageous and it is desirable to maintain an enhanced level of percutaneous adsorption for an extended time period.

According to the present invention there is provided a two-phase composition for topical application, wherein the two phases are intended to be mixed together on or immediately prior to application, comprising:

a first liquid phase containing a drug dissolved therein and comprising a topically acceptable solubiliser; and a second liquid phase, physically and/or chemically different from the first phase but miscible therewith on admixture, optionally containing the same drug dissolved therein and comprising a topically acceptable carrier; the composition of the first and second liquid phases being such that each has a different lipophilicity and each confers a different saturated solubility on the drug; the concentration of drug in each phase in which it is present and the composition of each of the first and second liquid phases being such that, on admixture of the phases, the total drug concentration in the mixture thus formed is greater than the saturated drug concentration in the same mixture, whereby the said mixture is supersaturated with the drug; characterised in that the topically acceptable carrier of the second liquid phase comprises a first component which is water and a second component which has a lipophilicity intermediate between that of water and the solubiliser of the first liquid phase.

The term drug is used herein to denote topically active substances including pharmaceutically active substances and substances conferring therapeutic and/or cosmetic benefit.

30

The term liquid is used herein to denote materials of varying consistency ranging from lotions to viscous materials, in particular creams and gels.

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It will be appreciated that compositions of the invention are not limited with respect to the physical nature of the product obtained on mixing the two liquid phases, provided that the first and second liquid phases are miscible.

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The second liquid phase need not contain any drug, provided that the product obtained on admixture of the two phases is supersaturated with respect to drug. Each phase may contain one or more drugs in amounts such that the resultant product mixture is supersaturated in one or more drugs.

Preferably, a composition of the invention has a first liquid phase which is saturated with drug. More preferably, a composition of the invention has a first liquid phase which is saturated with drug and a second liquid phase which contains no drug. The degree of saturation, and hence the rate of drug release from the resulting supersaturated drug preparation after mixing, can then be readily predicted from the saturated solubility curve for a given solubiliser/carrier system.

Due to the inefficiency of percutaneous absorption, highly supersaturated systems can be of great benefit. The rate of drug penetration in situ will depend largely on the degree of saturation, vis the ratio of supersaturated drug concentration to saturated drug concentration. A degree of saturation in excess of 1 is considered useful, and values from 2, for relatively slow penetration, to 10, for rapid penetration, are preferred. By means of the present invention very high degrees of saturation may be both obtained and moreover maintained over a substantial time period.

In a composition according to the invention, the relative proportion by weight of the first liquid phase to the second

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liquid phase is advantageously from 1:1 to 1:12, preferably from 1:2 to 1:8.

As used herein with respect to any composition of the invention, the term solubiliser denotes a liquid in which a drug has a higher saturated solubility than in an associated carrier.

Analogously, the term carrier denotes a liquid in which a drug has a lower saturated solubility than in an associated solubiser.

Suitably a solubiliser is a liquid in which a drug is readily soluble whilst a carrier is a liquid in which a drug has poor solubility.

Since water is a necessary component of the topically acceptable carrier of the second liquid phase, it will be readily appreciated that topically acceptable solubilisers suitable for use in compositions of the present invention are generally more lipophilic or less-polar liquids. The first liquid phase may comprise more than one such liquid.

Examples of suitable solubilisers include propylene glycol, 1,3-propylene diol, polyethylene glycol, ethanol, propanol, acetone, dimethylisosorbide, dimethylsulphoxide, benzyl alcohol, and other glycol, ether and ester solvents of similar polarity.

Preferred solubilisers are propylene glycol, polyethylene glycol and ethanol.

The second component of the topically acceptable carrier of the second liquid phase is a liquid miscible with water, suitably having a lipophilicity closer to that of water than that of solubiliser. Favourably the second component is not

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volatile at ambient, and particularly at body temperature.

Suitable liquids include glycerol and propylene glycol.

A preferred liquid is glycerol.

5

The second component may comprise up to 50% by weight of the topically acceptable carrier, suitably from 5 to 40% by weight and preferably from 10 to 25% by weight.

10 In a preferred composition of the invention, the solubiliser of the first liquid phase comprises a first component which is non-volatile and, a second component which is relatively more volatile at ambient, and particularly at body temperature. Favourably the second more volatile component
15 has comparable volatility to water. Suitable more volatile components include ethanol, isopropanol and acetone. A preferred more volatile component is ethanol. Suitably, a relatively more volatile second component comprises up to 50% by weight of the first liquid phase.

20

The invention also encompasses compositions in which a relatively more volatile solubiliser, for example ethanol, is present in the second liquid phase. The second liquid phase suitably comprises up to 20% by weight of such
25 relatively more volatile solubiliser, for example from 4% to 20% of such relatively more volatile solubiliser.

The incorporation of a more volatile solubiliser component with comparable volatility to water, further counteracts the
30 tendency for the degree of saturation in the supersaturated preparation, generated on mixing, to decline.

Co-evaporation of this more volatile component with water

further stabilises the lipophilicity (or polarity) of the resulting mixture and hence the drug saturated solubility.

Compositions of the invention may also contain an antinucleating agent. The antinucleating agent used in compositions according to the invention may be present in either or both of the said first and second liquid phases of the composition. Advantageously, it is present in at least the second phase and it may additionally be present in the first phase. In any event, when the two phases are mixed to provide a superaturated solution, the antinucleating agent will, of course, be present in the resulting solution.

The antinucleating agent may be present in an amount of up to 10% by weight, suitably in an amount of up to 5.0% by weight, advantageously from 0.01 to 2.0% by weight, and preferably from 0.1 to 0.5% by weight, based on the total weight of the composition.

The antinucleating agent should be soluble or dispersible in the phase or phases in which it is present and, of course, in the resulting mixed solution.

Examples of suitable antinucleating agents are hydroxyalkylcelluloses, such as hydroxypropylmethylcellulose and hydroxypropylcellulose, polyvinylpyrrolidone, polyacrylic acid, and derivatives thereof. A mixture of two or more different antinucleating agents may be used. In the event that an antinucleating agent is included in each of the first and second liquid phases of the composition, the same or different antinucleating agents may be included in each phase.

The choice of suitable antinucleating agent will depend both on the particular drug and the choice of solvent materials

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making up the first and second phases, but suitable anti-nucleating agents can readily be selected by simple experiment. This may be done, for example, by preparing samples of the desired final supersaturated drug solution; adding a selection of anti-nucleating agents (in say 1% by weight concentration), one to each sample; allowing the samples to stand for say 2 hours; and noting which solutions have remained clear.

- 10 Each of the first and second liquid phases may be thickened with a suitable thickening or gelling agent of either natural or synthetic origin. Examples of thickening and gelling agents are natural gums, tragacanth, carageen, pectin, agar, alginic acid, cellulose ethers and esters, xanthan gum, guar and locust bean gum, bentonite (a colloidal hydrated aluminium silicate), veegum (colloidal magnesium aluminium silicate), laponite (a synthetic hectorite), polyvinyl alcohol, Pluronic (a Tradename), Aerosil (a Tradename colloidal silica), and Carbopol (a Tradename).

Certain thickening agents may require the addition of an adjunct which serves to activate the thickening mechanism. For example, amines are commonly used in conjunction with Carbopol suspensions.

Preservatives including anti-oxidants and UV absorbers, and other adjuvants may also be added to one or both phases.

- 30 Compositions of the invention may be prepared by processes well known in the art of pharmaceutical formulation, for example by admixture, using appropriate equipment and techniques, of the components present in each of the first and second liquid phases.

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The composition of the invention may be packaged into a twin compartment pack ready for topical application by the user or patient. The user or patient would normally apply the two phases simultaneously to the treatment area and then mix the phases together in situ to create the supersaturated drug system.

The two phases may also be mixed in the pack by breaking a membrane or seal separating the first and second phases, thus creating a supersaturated solution in the pack, prior to application. Suitable packs for such purposes are commercially available.

Compositions of the invention are suitable for any medical, cosmetic or other treatment of the body surface, including the skin, scalp, nails and oral mucosa. Compositions of the invention may also be of value in delivering drugs to the systemic system by the so-called transdermal route, in which a drug is applied topically for absorption through the skin for systemic therapy.

Compositions of the invention provide a means by which many drugs which exhibit poor topical absorption, or which are required at high dosage levels, can be administered effectively in a transdermal system. Accordingly, the invention, provides a transdermal device containing a composition according to the invention.

Since a composition of the invention consists of two distinct phases, such a device will suitably comprise two compartments, for separate storage of the two phases divided by a breakable seal or membrane to allow for mixing of the two phases prior to attachment of the device to the skin surface.

35

In a further aspect of the invention there is provided a method for topical treatment of the human or animal body

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which comprises applying thereto an effective amount a pharmaceutical composition according to the invention.

Suitable drugs for use in the composition and method of the invention are many and varied and include agents having the following activities:

anti-pruritics, anti-bacterials, anti-septics, anti-virals, anti-fungals, anti-psoriasis agents, anti-acne agents, anti-dandruff agents; anti-histamines, local anaesthetics, analgesics, anti-inflammatories, anti-plaque agents, beta-adrenoceptor blockers, broncho-spasm relaxants, anti-angina agents, anti-travel sickness agents, decongestants, anti-tussives, anti-coagulants, head-lice treatments, anti-baldness treatments, and substances which have a beneficial effect on the skin for example in the treatment of photoageing and UV-damaged skin.

Suitable drug types include, for example, steroids, non-steroidal anti-inflammatory agents, imidazoles and retinoids, for example all-trans retinoic acid (tretinoin), 13-cis retinoic acid (isotretinoin) and retinyl esters such as retinyl propionate.

The following Examples illustrate the invention. They provide two-phase formulations which on mixing the two phases generate supersaturated solutions.

In each of Examples 1, 2, 5, 6, 7, 8, 9 and 10 a supersaturated solution is formed by mixing one part of the first phase with seven parts of the second phase. In Examples 3 and 4, a supersaturated solution is formed by mixing one part of the first phase with four parts of the second phase.

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In addition to the constituents described in the Examples, the first and second phases may each contain, as appropriate and where not already indicated, adjuvants such as antinucleating agents, for example HPC, HPMC and PVP; antioxidants, for example butylated hydroxyanisole; preservatives, for example phenoxytol; gelling or thickening agents, for example Carbopol 980 with a suitable neutralising agent such as trisamino for a non-aqueous phase or sodium hydroxide for an aqueous phase; and UV absorbers, for example benzophenone-3.

The following abbreviations are used:

| | | |
|--------|---|------------------------------|
| PEG | : | polyethylene glycol |
| 15 PVP | : | polyvinylpyrrolidone |
| HPMC | : | hydroxypropylmethylcellulose |
| HPC | : | hydroxypropylcellulose |

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Example 1

| | | <u>% w/w</u> | |
|----|----------------|------------------------|-------|
| 5 | First Phase : | Hydrocortisone Acetate | 0.20 |
| | | Propylene Glycol | 49.40 |
| | | PEG 400 | 49.40 |
| | | PVP | 1.00 |
| 10 | Second Phase : | HPMC | 0.50 |
| | | Glycerol | 38.00 |
| | | Water | 61.50 |

Example 2

| | | | |
|----|----------------|------------------------|-------|
| 15 | First Phase : | Hydrocortisone Acetate | 0.16 |
| | | PEG 400 | 99.84 |
| 20 | Second Phase : | Glycerol | 20.00 |
| | | Water | 80.00 |

Example 3

| | | | |
|----|----------------|------------------|-------|
| 25 | First Phase : | Indomethacin | 0.25 |
| | | Propylene glycol | 99.75 |
| | Second Phase : | Glycerol | 40.00 |
| | | Water | 60.00 |

Example 4

| | | | |
|----|----------------|--------------------|-------|
| 30 | First Phase : | Retinyl Propionate | 0.01 |
| | | PEG 400 | 99.99 |
| 35 | Second Phase : | Propylene Glycol | 40.00 |
| | | Water | 60.00 |

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Example 5

| | | | |
|----|----------------|------------------------|-------|
| 5 | First Phase : | Hydrocortisone Acetate | 0.20 |
| | | Propylene Glycol | 49.40 |
| | | Ethanol | 49.40 |
| | | PVP | 1.00 |
| 10 | Second Phase : | HPMC | 0.50 |
| | | Glycerol | 38.00 |
| | | Water | 61.50 |

Example 6

| | | | |
|----|----------------|------------------------|-------|
| 15 | First Phase : | Hydrocortisone Acetate | 0.20 |
| | | Propylene Glycol | 49.40 |
| | | Ethanol | 49.40 |
| | | PVP | 1.00 |
| 20 | Second Phase : | HPMC | 0.50 |
| | | Glycerol | 19.00 |
| | | Water | 80.50 |

Example 7

| | | | |
|----|----------------|------------------------|--------------|
| 25 | | | <u>% w/w</u> |
| | First Phase : | Hydrocortisone Acetate | 0.16 |
| | | PEG 400 | 99.84 |
| 30 | Second Phase : | Glycerol | 17.00 |
| | | Water | 68.50 |
| | | Ethanol | 14.50 |

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Example 8

| | | |
|---------------|------------------|-------|
| First Phase : | Retinoic Acid | 0.02 |
| | Propylene Glycol | 99.98 |

5

| | | |
|----------------|----------|-------|
| Second Phase : | Glycerol | 12.00 |
| | Water | 72.00 |
| | Ethanol | 16.00 |

10 Example 9

| | | |
|---------------|------------------------|-------|
| First Phase : | Hydrocortisone Acetate | 0.20 |
| | Ethanol | 99.80 |

| | | |
|-------------------|----------|-------|
| 15 Second Phase : | HPMC | 0.50 |
| | Glycerol | 19.00 |
| | Water | 80.50 |

Example 10

20

| | | |
|---------------|---------------|-------|
| First Phase : | Retinoic Acid | 0.02 |
| | HPC | 1.00 |
| | PEG 400 | 98.98 |

| | | |
|-------------------|------------------|-------|
| 25 Second Phase : | Glycerol | 5.80 |
| | Ethanol | 15.50 |
| | Propylene Glycol | 3.80 |
| | HPMC | 1.00 |
| | Water | 73.90 |

Claims

1. A two-phase composition for topical application,
wherein the two phases are intended to be mixed
together on or immediately prior to application,
comprising:

a first liquid phase containing a drug dissolved therein and comprising a topically acceptable solubiliser; and a second liquid phase, physically and/or chemically different from the first phase but miscible therewith on admixture, optionally containing the same drug dissolved therein and comprising a topically acceptable carrier; the composition of the first and second liquid phases being such that each has a different lipophilicity and each confers a different saturated solubility on the drug; the concentration of drug in each phase in which it is present and the composition of each of the first and second liquid phases being such that, on admixture of the phases, the total drug concentration in the mixture thus formed is greater than the saturated drug concentration in the same mixture, whereby the said mixture is supersaturated with the drug; characterised in that the topically acceptable carrier of the second liquid phase comprises a first component which is water and a second component which has a lipophilicity intermediate between that of water and the solubiliser of the first liquid phase.

2. A composition as claimed in claim 1 in which the topically acceptable solubiliser is selected from propylene glycol, 1,3-propylene diol, polyethylene glycol, ethanol, propanol, acetone, dimethylisosorbide, dimethylsulphoxide, benzyl alcohol and other glycol, ether and ester solvents of similar

polarity.

3. A composition as claimed in claim 2 in which the
solubiliser is propylene glycol, polyethylene glycol,
5 ethanol or mixtures thereof.
4. A composition as claimed in any one of claims 1 to 3
in which the second component of the topically
acceptable carrier of the second liquid phase
10 comprises up to 50% by weight of the topically
acceptable carrier.
5. A composition as claimed in claim 4 in which the
second component of the topically acceptable carrier
15 is glycerol or propylene glycol.
6. A composition as claimed in any one of claims 1 to 6
in which the topically acceptable solubiliser of the
first liquid phase comprises a first component which
20 is non-volatile and a relatively more volatile second
component.
7. A composition as claimed in claim 6 in which the
relatively more volatile second component has
25 comparable volatility to water.
8. A composition as claimed in claim 7 in which the
relatively more volatile second component comprises up
to 50% by weight of the first liquid phase.
30
9. A composition as claimed in any one of claims 1 to 8
in which the second liquid phase comprises up to 20%
by weight of a relatively more volatile second
component as defined in claim 7.
35
10. A composition as claimed in any one of claims 6 to 9
in which the relatively more volatile second component

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is ethanol, isopropanol or acetone.

11. A composition as claimed in any one of claims 1 to 10
in which the first liquid phase is saturated with
5 drug.
12. A composition as claimed in any one of claims 1 to 11
in which the relative proportion by weight of the
first liquid phase to the second liquid phase is from
10 1:1 to 1:12.
13. A composition as claimed in any one of claims 1 to 12
in which the degree of saturation or admixture of the
first and second liquid phases is in the range 2 to
15 10.
14. A composition as claimed in any one of claims 1 to 11
in which the drug is a steroid, a non-steroidal anti-
inflammatory agent, an imidazole or a retinoid.
20
15. A twin compartment pack containing a composition as
defined in any one of claims 1 to 14, the first liquid
phase being in one compartment and the second liquid
phase being in the other compartment.
25
16. A transdermal device containing a composition as
defined in any one of claims 1 to 14.
17. A method for topical treatment of the human or animal
30 body which comprises applying thereto an effective
amount of a pharmaceutical composition as defined in
any one of claims 1 to 14.
18. A two-phase composition substantially as hereinbefore
35 described with reference to any one of the Examples.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 91/02064

| | | |
|---|---|-------------------------------------|
| I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ | | |
| According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 9/08 | | |
| II. FIELDS SEARCHED | | |
| Minimum Documentation Searched ⁷ | | |
| Classification System | Classification Symbols | |
| Int.C1.5 | A 61 K | |
| Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸ | | |
| | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ | | |
| Category ¹⁰ | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ |
| X | EP,A,0151953 (BEECHAM GROUP PLC) 21 August 1985, see claims 1,2,4-6,8,9; page 1, line 30 - page 2, line 7; page 2, lines 10-12, 18-28; page 3, lines 6-16, 21-22, 26-29; page 4, line 24 - page 5, line 13; page 6, the whole page ---- | 1-16 |
| X | EP,A,0272045 (BEECHAM GROUP PLC) 22 June 1988, see claims 1,7,9; page 3, lines 5-26, 45-55; page 4, lines 13-19 (cited in the application) ----- | 1-16 |
| <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div> | | |
| IV. CERTIFICATION | | |
| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report | |
| 20-01-1992 | 13. 02 92 | |
| International Searching Authority | Signature of Authorized Officer | |
| EUROPEAN PATENT OFFICE | Nicole De Bie | |

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 is directed to a method of treatment of the human or animal body the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out specifically.
3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This international Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9102064

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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP-A- 0151953 | 21-08-85 | AU-B- 576344 | 25-08-88 |
| | | AU-A- 3800885 | 01-08-85 |
| | | CA-A- 1249520 | 31-01-89 |
| | | JP-A- 60174715 | 09-09-85 |
| | | US-A- 4940701 | 10-07-90 |
| | | US-A- 4767751 | 30-08-88 |
| ----- | | | |
| EP-A- 0272045 | 22-06-88 | AU-B- 609756 | 09-05-91 |
| | | AU-A- 8227587 | 16-06-88 |
| | | JP-A- 63179821 | 23-07-88 |
| | | US-A- 4940701 | 10-07-90 |
| ----- | | | |